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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/736,769

12/16/2003

Scott W. Altmann

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04/17/2006

SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
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EXAMINER

LIU, SAMUEL W

ART UNIT

PAPER NUMBER

1653

DATE MAILED: 04/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/736,769	Applicant(s) ALTMANN ET AL.	
	Examiner Samuel W. Liu	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 February 2006 and 07 April 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-60 is/are pending in the application.
- 4a) Of the above claim(s) 3-39 and 59 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,50-58 and 60 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. <u>4/7/06</u> . |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>2/3/06, 6/18/04 & .</u> | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

Status of claims

Claims 1-60 are pending.

The amendment filed 3/26/06 which amends claims 1-2 and adds claims 50-60 has been entered. And, the applicants' request (filed 3/26/06) for extension of time of one month has been entered.

Election/Restrictions

Applicant's election (filed 2/3/06) of Group I, claims 1-2 is acknowledged. During communication with applicants' representative Thomas Triolo on April 7, 2006, clarification for election of the invention has been made based on the amended claim 1 directed to instant SEQ ID NO:4 which is not presented in the previous claims (before the amendment) of Group 1. Herein, Examiner agrees to examine Group I drawn to said SEQ ID NO:4 (see also the Interview Summary attached herein and the Interview Summary mailed 2/16/06).

Because in the response (filed 2/3/06) and during the telephonic interview (4/7/06) applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 3-49 are withdrawn from consideration by the examiner, as being drawn to a non-elected invention. New claim 59 is also withdrawn from consideration because the claim is directed to a polypeptide comprising SEQ ID NO:4 *complexed with an antibody*, which is patentably distinct from the elected polypeptide comprising SEQ ID NO:4.

New claims 50-58 and 60 are drawn into the elected Group I. Hence, pending claims 1-2 and 50-58 and 60 are examined in this Office action.

Claims/Specification Objections

The disclosure is objected to because of the following informalities:

On page 42, line 33, "FACS" should be spelled out for the first instance of use; see also page 43, line 1, "BODIP"; line 6, "EGFP" and line 22, "FLAG"; and page 48, line 20, "FCS".

On page 42, lines 18-19, "SEQ ID NO 1" should be changed to "SEQ ID NO:1".

On page 45, line 21, "SEQ ID NO: 39-42" should be changed to "SEQ ID NOs:39-42".

On page 61, line 16, asterisks "*****" should be deleted.

IDS

The references listed in the IDS filed 2/3/06, the IDS filed 6/18/04, and the IDS filed 5/18/04 have been considered by Examiner.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1-2, 50-58 and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 lacks functional language (e.g., cholesterol binding, as described in paragraph [0007]). It is of note that the instant SEQ ID NO:4 membrane protein (NPC1L1) possesses a sterol-sensing domain (SSD) having a role in sensing cholesterol levels through a mechanism

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which involves direct cholesterol binding. Incorporation of the functional parameter is thus required.

Claim 50 recites "... comprising a polypeptide selected from ... "; the recitation is not apparent as to whether or not the recited polypeptide refers to any polypeptide in addition to the SEQ ID NO:4 polypeptide and "another polypeptide" set forth in claim 2 from which claim 50 depends.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 2 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a isolated polypeptide having cholesterol binding property comprising instant SEQ ID NO:4, does not reasonably provide enablement for any fusion polypeptide comprising the SEQ ID NO:4 and any heterologous polypeptide/protein.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546(BPAI 1986). They include the nature of the invention, the state of the art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

(1) The scope of the claims/(2) The nature of the invention

The claim are broadly drawn to a chimeric macromolecule comprising fusion between a heterologous polypeptide and the instant full-length SEQ ID NO:4 protein having 1,332 amino

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acid residues. The current invention is directed to a cholesterol-binding protein which is membrane-bound (hydrophobic) and glycosylated wherein apart from that the SEQ ID NO:4 protein has 13 transmembrane spanning segments, it also comprises a sterol-sensing domain (SSD); said protein belongs to Niemann-pick C (NPC) family.

It has been shown that NPC2 protein fusion with His₆-GST, when expressed in *E.coli*, is insoluble, i.e., aggregated and inactive (see page 269, the left column, the 1st paragraph, Blom et al. (2003) *Human Mol. Genet.* 12, 257-272). Reconstitution of such large membrane protein, i.e., the instant SEQ ID NO:4 protein consisting of 1,332 amino acids (~ 150 KDa) and retention of biological activity of the infused full-length SEQ ID NO:4 protein requires a large quantity of experimentation. Because the specification does teach the “another polypeptide” (i.e., heterologous polypeptide), the scope of claims is outside the bounds of the enablement and would have resulted in the necessity of undue experimentation.

(3) The unpredictability of the art:

As stated above, the biological activity of any fusion protein comprising the heterologous polypeptide/protein would render the fused SEQ ID NO:4 membrane protein (high molecular weight) unfold or/and aggregated. There is insufficient teaching as to maintaining the SEQ ID NO: 4 proper folded in a chimeric state (fusion) and retaining the biological activity thereof. Thus, structure and function of the fusion protein in this regard is unpredictable.

(4) The state of the prior art:

The general knowledge and level of skilled in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure insufficiently describes common attribute and characteristics that identify the functional chimera

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macromolecule comprising the SEQ ID NO:4 and the heterologous protein (e.g., having high molecular weight), the specification needs to provide sufficient guidance to be considered enabling for the claimed invention.

(5) The quantity of experimentation necessary:

In the absence of working examples with regard to the genus stated above, unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. The quantity of experimentation would be large and unpredictable. One skilled in the art would be required to carry out an undue experimentation for screening and characterizing the properly folded and biological active fusion protein which has at least over 1,332 amino acids and is larger than approximately 150 KDa.

(6) The relative skill of those in the art:

In view of the preceding factors (1-5), the level of skill in this art is high and requires at least a molecular biologist with several years of experience in mutagenesis, molecular biology as well as knowledge in recombinant technology and steroid biochemistry. Yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable. An unduly level of skill is needed for the skilled artisan in order to make and characterize the claimed “giant” and hydrophobic fusion molecule. Said fusion protein tends to be aggregated in aqueous solution.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view of the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and

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the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Thus, the amount and level of experimentation needed is undue.

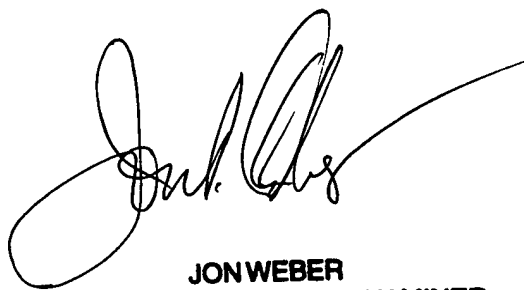
Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.



Samuel W. Liu, Ph.D.
Art Unit 1653, Examiner
April 7, 2006



JON WEBER
SUPERVISORY PATENT EXAMINER